National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: April 2018

AVXS-101 for spinal muscular atrophy

NIHRIO (HSRIC) ID: 13672 NICE ID: 9395

LAY SUMMARY

Spinal muscular atrophy (SMA) is a progressive, lethal disease that gets worse over time. Patients with the disease lack a gene that produces a protein called 'survival motor neuron' (SMN) protein, which is essential for the normal functioning and survival of motor neurons (nerves from the brain and spinal cord that control muscle movements). Without this protein, the motor neurons deteriorate and eventually die. SMA is divided into 4 subtypes, based on when the disease starts and how severe it is. SMA is an inherited disease and is usually diagnosed within the first few months of life for the most severe subtype (type 1). SMA causes the muscles to fall into disuse, leading to muscle wasting (atrophy) and weakness, and in its most common form (SMA type 1), loss of swallowing function, breathing failure and (absent treatment) death within the first few years of life.

AVXS-101 is a gene replacement therapy, made of a virus that has been modified to contain the primary gene for the SMN protein, which is lacking (or mutated) in patients with SMA. When injected into the patient, the virus is expected to carry the gene into the nerve cells, enabling them to start producing sufficient amounts of SMN. This is expected to improve the survival and function of the motor neurons, and so preserve muscle function. AVXS-101 is thought to address the root cause of SMA and therefore, if licensed, may offer an additional treatment option for patients with spinal muscular atrophy.

This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

TARGET GROUP

Spinal muscular atrophy (type 1)

TECHNOLOGY

DESCRIPTION

AVXS-101 (onasemnogene abeparvovec) is a gene replacement therapy medicinal product that introduces recombinant DNA into a patient's own cells to address the genetic defect and modulate protein production and cellular function. AVXS-101 utilizes a non-replicating adeno-associated virus subtype 9 (AAV9), capsid to deliver a functional copy of a human survival motor neuron (SMN) gene to the patient's own cells without modifying the existing DNA of the patient. SMN is a critical protein for normal motor neuron signalling and function and enables rapid onset of effect. The AAV9 capsid crosses the blood-brain barrier, thus allowing for intravenous (IV) administration. A cytomegalovirus enhanced chicken beta-actin hybrid promoter is a constitutive promoter that has been observed to increase transgene expression from AAV vectors compared to other promoters.[1,2]

In the phase III clinical trial (STR1VE; NCT03306277), AVXS-101 is administered one-time as IV infusion at a therapeutic dose[3]. Another phase III clinical trial (STRIVE-EU; NCT03461289) includes a screening period, a gene replacement therapy period, and a follow-up period. During the screening period (days -30 to -2), patients will complete screening procedures to determine eligibility for trial enrolment. Patients who meet the entry criteria will enter the in-patient gene replacement therapy period (day -1 to day 3). On day -1, patients will be admitted to the hospital for pre-treatment baseline procedures. On day 1, patients will receive a one-time 30-60-minute IV infusion of AVXS-101, and will undergo in-patient safety monitoring over the next 48 hours. Patients may be discharged 48 hours after the infusion, based on Investigator judgment. During the outpatient follow-up period (days 4 to end of trial at 18 months of age), patients will return at regularly scheduled intervals for efficacy and safety assessments until the end of trial when the patient reaches 18 months of age.[4]

AVXS-101 does not currently have Marketing Authorisation in the EU for any indication.

AVXS-101 is being developed for all types of SMA.

INNOVATION and/or ADVANTAGES

Promising positive phase I trial results demonstrate that AVXS-101 is a breakthrough product for the treatment of SMA. Early intervention before significant loss of motor neuron function is expected to enable the patient to develop stronger musculature that may be observed as (1) an increase in motor function resulting in the ability to achieve developmental milestones, (2) the ability to breath without support, (3) the ability to swallow (4) the ability to achieve functional independence and (4) significantly improved event-free survival.[5]

It is believed that gene replacement therapy is a well-suited approach for the treatment of spinal muscle atrophy (SMA) due to the monogenic nature of the disease, meaning it is caused by the deletion of, or mutations in, a single gene. AVXS-101 is designed to prevent further muscle degeneration caused by SMA through the delivery of a fully functional human SMN gene into target motor neuron cells, the production of sufficient levels of SMN protein required to improve motor neuron function, and the rapid onset of effect in addition to sustained SMN protein expression.[2]

AVXS-101 is believed to address the root cause of SMA, and if licenced will offer an additional treatment option for people with SMA.

DEVELOPER

AveXis, Inc.

REGULATORY INFORMATION/ MARKETING PLANS

AVXS-101 is a designated orphan drug in the EU/USA for spinal muscular atrophy.[6,7]

AVXS-101 was granted PRIME status for spinal muscular atrophy type 1 by the EMA in January 2017.[8]

AVXS-101 was designated Breakthrough Therapy for spinal muscular atrophy type 1 by the FDA in July 2016.[9]

PATIENT GROUP

BACKGROUND

SMA is a genetic condition that causes muscle weakening and problems with movement. It is a serious condition that worsens over time.[10] This neuromuscular disease is caused by a genetic defect in the SMN1 gene, leading to the loss of motor neurons (nerves from the brain and spinal cord that control muscle movements) and resulting in progressive muscle weakness and paralysis. SMA is an inherited disease. In most cases, a child can only be born with SMA if both parents have a faulty gene that causes the condition.[2,6]

SMA is divided into sub-categories – SMA types 1, 2, 3, and 4 – based on disease onset and severity, which generally correlate to SMN protein levels.[2,6] SMA type 1 develops in babies less than six months old and is the most severe type (severe progressive muscle weakness and atrophy resulting in functional limitations, swallowing dysfunction, ventilatory dysfunction and failure, premature death in most in most cases by 2 years of age); type 2 describes children who develop symptoms in late infancy and sit but never walk independently; type 3 describes children who are able, at least temporarily, to walk, with symptoms typically developing after 18 months of age; type 4 affects adults and usually causes less severe problems.[10] Typical symptoms of SMA include weak arms and legs, movement problems, twitching or shaking muscles, bone and joint problems, problems swallowing and breathing difficulties.[10,11]

CLINICAL NEED and BURDEN OF DISEASE

SMA affects an estimated 1 in 6,000 to 1 in 10,000 births worldwide.[12] In 2015, SMA affected less than 0.4 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 21,000 people.[6] The Genetic Alliance UK reported round 900 children with SMA in the UK.[13] It is estimated that in England, approximately 89 are born with SMA per year (based on 2015 statistics), and it was estimated that in 2012, 50 people were living with SMA Type 1, 625 were living with SMA Type 2, and 1,750 were living with SMA Type 3.[12]

It is estimated that 1 in 40 people in the UK is a carrier of the genetic mutation that causes SMA. When two carriers have a child, there is a 25% risk that the child will have SMA.[14]

In the UK in 2016-17, there were 4,758 finished consultant episodes (FCE) for spinal muscular atrophy and related symptoms (ICD 10 G12), resulting in 3,036 hospital admissions and 29,610 FCE bed days.[15]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Nusinersen for treating spinal muscular atrophy (TA10281). Expected November 2018.
- NICE guideline. Motor neurone disease: assessment and management (NG42). February 2016.
- NICE quality standard. Motor neurone disease (QS126). July 2016.
- NICE interventional procedures guidance. Intramuscular diaphragm stimulation for ventilator-dependent chronic respiratory failure caused by motor neurone disease (IPG593). September 2017.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Urgent Clinical Commissioning Policy Statement: Nusinersen for genetically confirmed Spinal Muscular Atrophy (SMA) type 1 for eligible patients under the Expanded Access Programme (EAP). 170038P. March 2018.
- NHS England. Service Specification: Neuropathology. 16074/S.
- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a
- NHS England. 2013/14 Standard Contract for Diagnostic Service for Rare Neuromuscular Disorders (All ages). D04/S(HSS)/a

OTHER GUIDANCE

- Technical standards and guidelines for spinal muscular atrophy testing (2011)[16]
- Standards of care for spinal muscular atrophy (2008)[17]
- Consensus statement for standard of care in spinal muscular atrophy (2007)[18]

CURRENT TREATMENT OPTIONS

In the UK, SMA is currently managed through multidisciplinary supportive care. Treatment usually follows guidelines from the International Standards of Care Committee for Spinal Muscular Atrophy.[17] Supportive care strategies aim to minimise the impact of disability, address complications and improve quality of life. These may involve respiratory, gastroenterology, and orthopaedic care, as well as nutritional support, physiotherapy, assistive technologies, occupational therapy and social care.[19]

Nusinersen (Spinraza) has a marketing authorisation in the UK for the treatment of SMA.[19] It is, however, not routinely commissioned by the NHS (as of Jan 2018) and only available to select NHS patients through an expanded access programme.[20]

EFFICACY and SAFETY	
Trial	STR1VE; AVXS-101-CL-303, NCT03306277; patients < 6 months of age; single-dose gene replacement therapy; phase III
Sponsor	AveXis, Inc.
Status	Recruiting
Source of Information	Trial registry[3]
Location	USA
Design	Single-group assignment, open-label, single-arm
Participants	N=15 (up to 20 planned); up to 180 days; SMA type 1 based on gene mutation analysis with bi-allelic SMN1 mutations and 1 or 2 copies of SMN2; swallowing evaluation test performed prior to administration of gene replacement therapy
Schedule	Patients receive one-time intravenous administration of AVXS-101 at the therapeutic dose
Follow-up	Not reported
Primary Outcomes	• Achievement of independent sitting [Time Frame: 18 months of age visit] • Event-free survival [Time Frame: 14 months of age visit]
Secondary Outcomes	• Ability to thrive [Time Frame: Through 18 months of age] • Ventilatory support independence [Time Frame: Through 18 months of age]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date reported as March 2020.

Trial	STRIVE-EU; AVXS-101-CL-302, NCT03461289; patients < 6 months of age; single-dose gene replacement therapy; phase III
Sponsor	AveXis, Inc.
Status	Not yet recruiting
Source of Information	Trial registry[4]
Location	8 EU countries (incl. UK)
Design	Single-group assignment, open-label, single-arm
Participants	N=30 (planned); up to 180 days; SMA type 1 based on gene mutation analysis with bi-allelic SMN1 mutations and 1 or 2 copies of SMN2; swallowing evaluation test performed prior to administration of gene replacement therapy
Schedule	The trial includes a screening period, a gene replacement therapy period, and a follow-up period. During the screening period (days -30 to -2), patients whose parent(s)/legal guardian(s) provide informed consent will complete screening procedures to determine eligibility for trial enrollment. Patients who meet the entry criteria will enter the in-patient gene replacement therapy period (day -1 to day 3). On day -1, patients will be admitted to the hospital for pre-treatment baseline procedures. On day 1, patients will receive a one-time IV infusion of AVXS-101, and will undergo in-patient safety monitoring over the next 48 hours. Patients may be discharged 48 hours after the infusion, based on Investigator judgment. During the outpatient follow-up period (days 4 to end of trial at 18 months of age), patients will return at regularly scheduled intervals for efficacy

	and safety assessments until the end of trial when the patient reaches 18 months of age. After the end of trial visit, eligible patients will be asked to rollover into the long-term follow up trial.
Follow-up	All post-treatment visits will be relative to the date on which gene replacement therapy is administered, except for the 14 and 18 months of age visits, which will be relative to the patient's date of birth.
Primary Outcomes	Sitting without support [Time Frame: Through 18 months of age]
Secondary Outcomes	Survival [Time Frame: Through 14 months of age]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date reported as November 2020.

Trial	START, NCT03421977; patients from AVXS-101-CL-101 study for continuous safety monitoring for up to 15 years; single-dose gene replacement therapy; long-term, safety follow up study
Sponsor	AveXis, Inc.
Status	Enrolling by invitation
Source of Information	Trial registry[21]
Location	USA
Design	Long-term, safety follow up study
Participants	N=15 (planned); Patients who received AVXS-101 in the AVXS-101-CL-101 gene replacement therapy clinical trial for SMA Type 1
Schedule	This is a long term, safety follow up study of patients in the AVXS-101-CL-101 gene replacement therapy clinical trial for SMA Type 1 delivering AVXS 101. Patients will roll over from the parent study into this long-term study for continuous safety monitoring for up to 15 years. The last visit of the parent study or early discontinuation from the parent study may serve as the visit at which the informed consent form process is conducted for the AVXS 101 LT-001 long term follow-up safety study. Patients will return annually for follow up study visits for five years, and then will be contacted via phone annually for ten years. Additionally, patient record transfers from their local physician and/or neurologist will be requested in conjunction with the annual study visits and phone contacts for review by the investigator. If the patient is unable to return to the original investigative site, the sponsor will arrange with the patients' local established physician to serve as an additional investigator to conduct the required assessments.
Follow-up	-
Primary Outcomes	Long-Term Safety [Time Frame: 15 years]
Secondary Outcomes	Not reported
Key Results	-

Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date reported as December 2033.

ESTIMATED COST and IMPACT

COST

The cost of AVXS-101 is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☐ Other

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☒ Reduced drug treatment costs

☐ Other increase in costs

☒ Other reduction in costs

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

REFERENCES

[1] Avexis. *2016 Annual Report to Stockholder*. Available from: http://investors.avexis.com/phoenix.zhtml?c=254285&p=irol-reportsAnnual [Accessed 28 March 2018]

[2] Avexis. *The only SMA gene therapy in human trials.* Available from: https://avexis.com/research-and-development [Accessed 28 March 2018]

[3] ClinicalTrials.gov. *Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1 (STR1VE)*. Available from: https://clinicaltrials.gov/ct2/show/NCT03306277 [Accessed 28 March 2018] Last updated 28 February 2018

[4] ClinicalTrials.gov. *Single-Dose Gene Replacement Therapy Clinical Trial for Patients With Spinal Muscular Atrophy Type 1 (STRIVE-EU)*. Available from: https://clinicaltrials.gov/ct2/show/NCT03461289 [Accessed 28 March 2018] Last updated 19 March 2018

[5] Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW,et al. *Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy.* N Engl J Med 2017;377:1713-1722

[6] European Medicines Agency. *Public summary of opinion on orphan designation - Adeno-associated viral vector serotype 9 containing the human SMN gene for the treatment of spinal muscular atrophy*. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Orphan_designation/2015/07/WC500190630.pdf [Accessed 28 March 2018]

[7] Spinal muscular Atrophy.info. *AveXis Receives Orphan Drug Status from the US Food and Drug Administration (FDA) for chariSMA for the Treatment of Spinal Muscular Atrophy*.

[8] Avexis. *AveXis Gene Therapy AVXS-101 Granted Access into EMA PRIME Program for Spinal Muscular Atrophy Type 1.* Available from: http://investors.avexis.com/phoenix.zhtml?c=254285&p=irol-newsArticle&ID=2240880 [Accessed 28 March 2018]

[9] Avexis. *AveXis Receives U.S. FDA Breakthrough Therapy Designation for AVXS-101 Gene Replacement Therapy for Spinal Muscular Atrophy Type 1*. Available from: http://investors.avexis.com/phoenix.zhtml?c=254285&p=irol-newsArticle&ID=2186665 [Accessed 28 March 2018]

[10] NHS choices. *Spinal muscular atrophy*. Available from: https://www.nhs.uk/conditions/spinal-muscular-atrophy-sma/ [Accessed 28 March 2018]

[11] Kolb SJ, Kissel JT. *Spinal muscular atrophy: a timely review.* Arch Neurol. 2011; 68(8):979-84

[12] Spinal Muscular Atrophy Support UK. *Population statistics & meeting NICE's HST criteria – our view.* Available from: http://www.smasupportuk.org.uk/population-statistics-and-meeting-nices-hst-criteria-our-view [Accessed 28 March 2018]

[13] National Institute for Health and Care Excellence. Nusinersen for treating spinal muscular atrophy - Single Technology Appraisal (STA) [Internet]. NICE 2018 [cited 14 March 2018]. Available from: https://www.nice.org.uk/guidance/gid-ta10281/documents/scope-consultation-comments-and-responses

[14] TreatSMA. *How many people have SMA?* Available from: https://www.treatsma.uk/sma/prevalence/ [Accessed 28 March 2018]

[15] NHS Digital, Hospital Episode Statistics for England. *Admitted Patient Care statistics, 2016-17*. Available from: https://digital.nhs.uk/catalogue/PUB30098 [Accessed 28 March 2018]

[16] Prior TW, Nagan N, Sugarman EA et al. Technical standards and guidelines for spinal muscular atrophy testing. *Genetics in Medicine* 2011 (13):7. Available from: https://doi.org/10.1097/GIM.0b013e318220d523

[17] Treat-NMD. *Standards of care for spinal muscular atrophy (2008)*. Available from: http://www.smasupportuk.org.uk/files/files/General%20Information%20and%20Support/sma_soc_brochure_en.pdf [Accessed 28 March 2018]

[18] Wang CH, Finkel RS, Bertini ES et al. Consensus statement for standard of care in spinal muscular atrophy. Journal of Child Neurology 2017 (22):8, 1027-1049. Available from: http://journals.sagepub.com/doi/pdf/10.1177/0883073807305788 [Accessed 28 March 2018]

[19] NICE. *Single Technology Appraisal – Nusinersen for treating spinal muscular atrophy, final scope*. Available from: https://www.nice.org.uk/guidance/gid-ta10281/documents/final-scope [Accessed 28 March 2018]

[20] Specialist Pharmacy Service. *Nusinersen*. Available from: https://www.sps.nhs.uk/medicines/nusinersen/ [Accessed 28 March 2018]

[21] ClinicalTrials.gov. *Long-Term Follow-up Study for Patients From AVXS-101-CL-101 (START).* Available from: https://clinicaltrials.gov/ct2/show/NCT03421977 [Accessed 28 March 2018] Last updated 5 February 2018